

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Julie Straub, David Altreuter, Howard Bernstein, Donald E. Chickering, III,
Sarwat Khattak, and Greg Randall

Serial No.: 10/053,929 Art Unit: 1618

Filed: January 22, 2002 Examiner: Blessing M. Fubara

For: *POROUS DRUG MATRICES AND METHODS OF MANUFACTURE THEREOF*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.131

Sir:

We, Julie Straub and Howard Bernstein, hereby declare that:

1. We are co-inventors of the above-identified application.
2. We conceived of and reduced to practice a method of forming microparticles that contain a diagnostic agent, which was subsequently described in U.S. Patent No. 6,565,885 to Tarara et al. This method involves spray drying a feed stock containing the diagnostic agent, a surfactant and a blowing agent. We conceived of and reduced to practice this method prior to September 29, 1997, as demonstrated by the attached copies of pages from a laboratory notebook (Exhibit A).

3. As noted in Exhibit A, the feed stock to the spray drying apparatus contained ammonium acetate, lecithin, (poly(ethylene glycol)-co-poly(lactide-co-glycolide) (75:25), D,L-

DECLARATION UNDER 37 C.F.R. § 1.131

poly(lactide), and air. This composition was emulsified using a VirTis homogenizer to form an emulsion, which was then spray dried using a small-scale lab spray dryer (see Exhibit A, page 14). The resulting microparticles had diameters ranging from 1-20 microns and were hollow with internal central-like voids containing the air bubble, as demonstrated by transmission electron microscopy (see Exhibit A, page 116). These microparticles were echogenic (see Exhibit A, page 105, injection 7).

4. I declare that all statements made herein of my own knowledge and belief are true and that all statements made on information and belief are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 03 Mar 06

Julie Straub
Julie Straub

Date: 03 Mar. 06

Howard Bernstein
Howard Bernstein

14 TITLE

Work continued to Page 13

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Herv T. B. L.

PROJECT NO.

BOOK NO.

Investigator: H. B. L.

Date:

Microsphere lot #: 302, 91-11

Microsphere Production
Process Room Conditions

Room Temp:	22°C
Room Humidity:	51.5% RH

Polymer Preparation

Polymer type 1:	186-PLA
Source & Lot no.:	BPE Lot # 504-14-14
Mass (g):	3.60 g
Polymer type 2:	D.L. - PLA
Source & Lot no.:	BPE Lot # 349.38
Mass (g):	3.61 g
Solvent Type:	MeOH
Source & Lot no.:	EA Lot no 35068
Volume:	240 mL
Surfactant type:	lecithin
Surf. concn/vol:	25 mg
Dissolution Meth.:	Stir bar
Dissolution Temp.:	Room temperature
Dissolution Time:	12:55
Reagent 1:	H ₂ O
Source & Lot no.:	House DZ
Amount, g/mL:	2 mL

Comments:

Discoloration in water as follows:
10.2 g in 40 mL of H₂O. Add 2 mL to polymer solution.

Aeration Methodology

Sonication:	None
Hom type:	
Frequency:	
Power:	
Temperature:	
Time:	
Time until spray:	
Spraying:	None
Gas type:	
Gas pressure:	
Temperature:	
Time:	
Time until spray:	
Homogenization:	VIENTIS
Blade type:	macro ultrasonic generator
Time:	1 minute (1:10)
Speed:	20 sec 2000
Temperature:	4°C bath
Time until spray:	~ 4 minutes
Comments:	

Spray Conditions

Cleaning Proc:	NaOH solution, MeOH, acetone, etc.
Nozzle type:	0.7 mm standard, vented B
Gas Pressure:	400 psi
Gas Flow rate:	600 L/H
Gas type:	N ₂ medical grade
Feed Flow rate:	112 g/min
Exit Temp.:	50°C
Start Time:	1:16
Finish Time:	1:28
Mass Recovered:	1663 - 1671 = 1.97
Yield (%):	2.7%

Process Conditions

	Start 1:17	Middle 1:24	Finish
Control Temp.:	24°C	24°C	24°C
Filter vacuum:	-40 mbar	-30 mbar	-30 mbar

Comments:

Did not tap inlet tube as I had done up a previous batch.

Drying Methodology

Type:	lyophilization, VIENTIS, 20 sec 2000
Total dry time:	Start 2:40 pm 9/12 - 4:00 pm 9/12
Mass recovered:	95.40 g 18.425 - 16.71 = 1.784
Yield (%):	13.425 g - 16.71 = 2.5%
Comments:	1.97 g in 40 mL dry ice, removed from dry ice at 1:35 At 1:35 pm 9/12, weight 16.71 g. Placed back in 20 mL vial. Removed from dry ice at 1:50 pm, 9/12.

Sizing Methodology

Room Temp.:	
Room Humidity:	
Sieving Time:	
Sieve size:	
Sieve type:	
Product recovered:	
Yield (%):	
Comments:	

Work continued to Page 15

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TITLE

TJU Study For

PROJECT NO

Acrophase
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Yucca Joffe University Hospital/Pharmaceutical Experiment 4/2/5 / 1/5

Confidential

Sample ID	Material	Volume	Weight	Volume	Weight	Preparation	Extraction	Extraction
						Preparation Comments	Solid	Over Time
W10001	Alcohol	10%	10%	10%	10%			
W10002	Alcohol	10%	10%	10%	10%			
W10003	Alcohol	10%	10%	10%	10%			
W10004	Alcohol	10%	10%	10%	10%			
W10005	Alcohol	10%	10%	10%	10%			
W10006	Alcohol	10%	10%	10%	10%			
W10007	Alcohol	10%	10%	10%	10%			
W10008	Alcohol	10%	10%	10%	10%			
W10009	Alcohol	10%	10%	10%	10%			
W10010	Alcohol	10%	10%	10%	10%			
W10011	Alcohol	10%	10%	10%	10%			
W10012	Alcohol	10%	10%	10%	10%			
W10013	Alcohol	10%	10%	10%	10%			
W10014	Alcohol	10%	10%	10%	10%			
W10015	Alcohol	10%	10%	10%	10%			
W10016	Alcohol	10%	10%	10%	10%			
W10017	Alcohol	10%	10%	10%	10%			
W10018	Alcohol	10%	10%	10%	10%			
W10019	Alcohol	10%	10%	10%	10%			
W10020	Alcohol	10%	10%	10%	10%			

Acrophase
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Sample ID	Material	Volume	Weight	Volume	Weight	Preparation	Extraction	Extraction
						Preparation Comments	Solid	Over Time
W10021	Alcohol	10%	10%	10%	10%			
W10022	Alcohol	10%	10%	10%	10%			
W10023	Alcohol	10%	10%	10%	10%			
W10024	Alcohol	10%	10%	10%	10%			
W10025	Alcohol	10%	10%	10%	10%			
W10026	Alcohol	10%	10%	10%	10%			
W10027	Alcohol	10%	10%	10%	10%			
W10028	Alcohol	10%	10%	10%	10%			
W10029	Alcohol	10%	10%	10%	10%			
W10030	Alcohol	10%	10%	10%	10%			
W10031	Alcohol	10%	10%	10%	10%			
W10032	Alcohol	10%	10%	10%	10%			
W10033	Alcohol	10%	10%	10%	10%			
W10034	Alcohol	10%	10%	10%	10%			
W10035	Alcohol	10%	10%	10%	10%			
W10036	Alcohol	10%	10%	10%	10%			
W10037	Alcohol	10%	10%	10%	10%			
W10038	Alcohol	10%	10%	10%	10%			
W10039	Alcohol	10%	10%	10%	10%			
W10040	Alcohol	10%	10%	10%	10%			

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Sample ID	Material	Volume	Weight	Volume	Weight	Preparation	Extraction	Extraction
						Preparation Comments	Solid	Over Time
W10041	Alcohol	10%	10%	10%	10%			
W10042	Alcohol	10%	10%	10%	10%			
W10043	Alcohol	10%	10%	10%	10%			
W10044	Alcohol	10%	10%	10%	10%			
W10045	Alcohol	10%	10%	10%	10%			
W10046	Alcohol	10%	10%	10%	10%			
W10047	Alcohol	10%	10%	10%	10%			
W10048	Alcohol	10%	10%	10%	10%			
W10049	Alcohol	10%	10%	10%	10%			
W10050	Alcohol	10%	10%	10%	10%			
W10051	Alcohol	10%	10%	10%	10%			
W10052	Alcohol	10%	10%	10%	10%			
W10053	Alcohol	10%	10%	10%	10%			
W10054	Alcohol	10%	10%	10%	10%			
W10055	Alcohol	10%	10%	10%	10%			
W10056	Alcohol	10%	10%	10%	10%			
W10057	Alcohol	10%	10%	10%	10%			
W10058	Alcohol	10%	10%	10%	10%			
W10059	Alcohol	10%	10%	10%	10%			
W10060	Alcohol	10%	10%	10%	10%			

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Sample ID	Material	Volume	Weight	Volume	Weight	Preparation	Extraction	Extraction
						Preparation Comments	Solid	Over Time
W10061	Alcohol	10%	10%	10%	10%			
W10062	Alcohol	10%	10%	10%	10%			
W10063	Alcohol	10%	10%	10%	10%			
W10064	Alcohol	10%	10%	10%	10%			
W10065	Alcohol	10%	10%	10%	10%			
W10066	Alcohol	10%	10%	10%	10%			
W10067	Alcohol	10%	10%	10%	10%			
W10068	Alcohol	10%	10%	10%	10%			
W10069	Alcohol	10%	10%	10%	10%			
W10070	Alcohol	10%	10%	10%	10%			
W10071	Alcohol	10%	10%	10%	10%			
W10072	Alcohol	10%	10%	10%	10%			
W10073	Alcohol	10%	10%	10%	10%			
W10074	Alcohol	10%	10%	10%	10%			
W10075	Alcohol	10%	10%	10%	10%			
W10076	Alcohol	10%	10%	10%	10%			
W10077	Alcohol	10%	10%	10%	10%			
W10078	Alcohol	10%	10%	10%	10%			
W10079	Alcohol	10%	10%	10%	10%			
W10080	Alcohol	10%	10%	10%	10%			

7/2/5

Samples weighed by Howard in Dry Box

on 7/2/5. All but the 94/082 and 94/083

Samples sent to Fairsberg on 7/2/5 by Air Mail

on dry ice / gel pack

SCIENTIFIC SUNDRY PRODUCTIONS CHICAGO 60605 Made in USA

SIGNATURE

John A. Shaw

Work continued to Page 8/105

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Henry T. Sol

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SCIENTIFIC BINDERY PRODUCTS INC. CHICAGO, ILL. 60646 U.S.A.

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4574 Jettabell 2.2. 1971

Acoustics

Notes

All samples will be prepared by vortexing and sonication.

All samples will be preweighed in 20 mL scintillation vials. Empty 20 mL scintillation vials will be brought.

Saline (0.9%) will be used instead of water for the bulk diluent in the pumping system. Preweighed samples of 16.2 g of NaCl will be brought out, and resealed in 1800 mL with water in a bottle. Two such bottles will be sent to TFL. A total of 30 NaCl vials will be brought.

Vehicle 1 = 0.5% Tween 20, 3% glycerol ← never used

Vehicle 2 = 0.9% P137, 54.6 mg/mL ethanol

1) System essentially same as 8/3/95 experiment, except 500 mL saline in bottles

2) Vehicle 2 (VF) was used

3) Yonguo Wu did the entire study

4) After injection of sample, sample was stirred, flow rate was then increased to 500-800 mL/min until echogenic material detected by the oscilloscope; Flow rate then dropped to 100-200 mL/min.

5) The "latex window" moved dramatically with each pulse

6) Tubing was manipulated to remove bubbles. At least once (prior to injection 4) this resulted in change of alignment. At that one detected time, the transducer was realigned.

7) Cleaning procedure: (1) water pumped to remove all material, then saline pumped in (2) water emptied, saline added + pumped through.

(2) System pumped dry, saline pumped in

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Work continued

105

8/84/105

Aspenhere

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Injection #	Sample ID/Material (Vehicle, mL)	Suspension Preparation	Echogenicity Initial	Echogenicity Over Time	Other Notes (if any)
1	Albunex 0.5	NA (100% albumin)	none - 1.5 min		yes
2	Albunex 0.5	NA (100% albumin)	slightly echogenic		yes
3	Albunex 0.5	"	slightly echogenic		yes
4	Albunex 0.5	"	not echogenic		no
5	VF-12	1/50/1/10	slightly echogenic	too white to film	yes
6	VF-12	1/50/1/10	slightly echogenic	decrease over time	yes
7	VF-12	1/50/1/10	echogenic (bubbling)	VF-12	yes
8	VF-12	1/50/1/10	echogenic	<1 min	yes
9	VF-12	1/50/1/10	echogenic	<1 min	yes
10	Albunex 0.5	NA (100% albumin)	slightly echogenic	decrease over time	yes
11	VF-12	1/50/1/10	not echogenic	not long	yes
12	VF-12	1/50/1/10	slightly echogenic	1-2 min	yes
13	VF-12	1/50/1/10	none		yes
14	VF-12	1/50/1/10	very faint	1-2 min	yes
15	VF-12	1/50/1/10	echogenic	1-2 min	yes
16	VF-12	1/50/1/10	echogenic	1-2 min	yes

Aspenhere

Confidential

Injection #	Sample ID/Material	Suspension Preparation	Echogenicity Initial	Echogenicity Over Time	Other Notes (if any)
17	VF-12	1/50/1/10	slightly echogenic	1-2 min	yes
18	VF-12	1/50/1/10	none		no
19	VF-12	1/50/1/10	none		no
20	VF-12	1/50/1/10	slightly echogenic	<1 min	yes
21	VF-12	1/50/1/10	very faint	<1 min	yes
22	VF-12	1/50/1/10	very faint	<1 min	yes
23	VF-12	1/50/1/10	very faint	<1 min	yes
24	VF-12	1/50/1/10	very faint	<1 min	yes
25	VF-12	1/50/1/10	very faint	<1 min	yes
26	VF-12	1/50/1/10	very faint	<1 min	yes
27	VF-12	1/50/1/10	very faint	<1 min	yes
28	VF-12	1/50/1/10	very faint	<1 min	yes
29	VF-12	1/50/1/10	very faint	<1 min	yes
30	VF-12	1/50/1/10	very faint	<1 min	yes
31	VF-12	1/50/1/10	very faint	<1 min	yes
32	VF-12	1/50/1/10	very faint	<1 min	yes

Steady
Run
TJU
on

SCIENTIFIC BIRNERY PRODUCTIONS CHICAGO 60605 Made in USA

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